26 August 2008

This supplement has been prepared to present scientific and technical news items that may be of more interest to technical personnel at RDT&E activities and the labs, or the medics rather than the broader readership of the basic CB Daily. Due to the nature of the material, the articles, if available online, are usually only available through subscription services thus making specific links generally unavailable. Thus, usually only the bibliographic citation is available for use by an activity's technical library.

Should you wish to be removed from this S&T Supplement address group, just send an email to one of the people listed at the bottom of this message. This will not affect your continued receipt of the CB Daily.

Chem-Bio News – Pandemic Influenza Supplement #25

1. AEROSOLIZED ANTIBIOTICS [AA] AND VENTILATOR-ASSOCIATED TRACHEOBRONCHITIS IN THE INTENSIVE CARE UNIT: *"In critically ill patients with ventilator-associated tracheobronchitis, AA decrease VAP [ventilator-associated pneumonia] and other signs and symptoms of respiratory infection, facilitate weaning, and reduce bacterial resistance and use of systemic antibiotics."*

2. THE EFFECT OF POPULATION STRUCTURE ON THE EMERGENCE OF DRUG RESISTANCE DURING INFLUENZA PANDEMICS: *This article discusses a model to assess the impact of population structure and stochasticity on the development of vaccine-resistant strains of influenza caused by a vaccination campaign.*

3. DELSITE SUBMITS IND APPLICATION FOR GELVAC NASAL POWDER INFLUENZA VACCINE: *"DelSite has announced that DelSite Biotechnologies, its wholly-owned subsidiary, has filed an investigational new drug application with the FDA for its lead product candidate GelVac nasal powder H5N1 influenza vaccine."*

4. INFLUENCE OF PRIOR INFLUENZA VACCINATION ON ANTIBODY AND B-CELL RESPONSES: *"Our findings suggest that the type of vaccine received in the prior year affects the serum antibody and the B-cell responses to subsequent vaccination. In particular, prior year TIV vaccination is associated with sustained higher HAI titer one year later but lower antibody response to new LAIV or TIV vaccination, and a lower effector B-cell response to new TIV but not LAIV vaccination."*

5. EVOLUTIONARY AND TRANSMISSION DYNAMICS OF REASSORTANT H5N1 INFLUENZA VIRUS IN INDONESIA: *"Moreover, our study also revealed significantly stronger diversifying selection on the M1 and PB2 genes in the lineages preceding and subsequent to the emergence of the reassortant viruses, respectively."*

6. H1N1 FLU VIRUSES GROWING MORE RESISTANT TO TAMIFLU: "*Thirty-one percent*

(242 of 788) of influenza A/H1N1 isolates from 16 countries that were tested in recent months carried a mutation associated with oseltamivir resistance, the WHO said."

7. SUBSTRATE CLEAVAGE ANALYSIS OF FURIN AND RELATED PROPROTEIN CONVERTASES. A COMPARATIVE STUDY: *"Our results also suggest that pathogens, including anthrax PA83 and the avian influenza A H5N1 (bird flu) hemagglutinin precursor, evolved to be as sensitive to PC proteolysis as the most sensitive normal human proteins."*

8. INFLUENZA IMMUNIZATION AND SUBSEQUENT DIAGNOSES OF GROUP A STREPTOCOCCUS [GAS]-ILLNESSES AMONG U.S. ARMY TRAINEES, 2002-2006: *"A strong protective effect was suggested for Army trainee influenza immunization on the diagnosis of GAS-illness."*

CB Daily Report

Chem-Bio News

AEROSOLIZED ANTIBIOTICS [AA] AND VENTILATOR-ASSOCIATED TRACHEOBRONCHITIS IN THE INTENSIVE CARE UNIT
Medical Devices & Surgical Technology Week
August 24, 2008

"In critically ill intubated patients, signs of respiratory infection often persist despite treatment with potent systemic antibiotics. The purpose of this study was to determine whether aerosolized antibiotics, which achieve high drug concentrations in the target organ, would more effectively treat respiratory infection and decrease the need for systemic antibiotics."

"Double-blind, randomized, placebo-controlled study performed from 2003 through 2004. The medical and surgical intensive care units of a university hospital. Critically ill intubated patients were randomized if: 1) >= 18 yrs of age, intubated for a minimum of 3 days, and expected to survive at least 14 days; and 2) had ventilator-associated tracheobronchitis defined as the production of purulent secretions (>= 2 mL during 4 hrs) with organism(s) on Gram stain. Of 104 patients monitored, 43 consented for treatment and completed the study. No patients were withdrawn from the study for adverse events. Aerosol antibiotic (AA) or aerosol saline placebo was given for 14 days or until extubation. The responsible clinician determined the administration of systemic antibiotics (SA). Patients were followed for 28 days. Primary: Centers for Disease Control National Nosocomial Infection Survey diagnostic criteria for ventilator-associated pneumonia (VAP) and clinical pulmonary infection score. Secondary: white blood cell count, SA use, acquired antibiotic resistance, and weaning from mechanical ventilation. Most patients had VAP at randomization. With treatment, the AA group had reduced signs of respiratory infection: reduced Centers for Disease Control National Nosocomial Infection Survey VAP (14/19; 73.6%) to (5/14; 35.7%) vs. placebo (18/24; 75%) to (11/14; 78.6%), reduction in clinical pulmonary infection score, lower white blood cell count at day 14, reduced bacterial resistance, reduced use of SA, and increased weaning (all p<= .05)."

"In critically ill patients with ventilator-associated tracheobronchitis, AA decrease VAP and other signs and symptoms of respiratory infection, facilitate weaning, and reduce bacterial resistance and use of systemic antibiotics."

The full article can be found in: (L.B. Palmer, et. al., "Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit". Critical Care Medicine, 2008;36 (7):2008-2013). Link not available.

Return to Top

THE EFFECT OF POPULATION STRUCTURE ON THE EMERGENCE OF DRUG RESISTANCE DURING INFLUENZA PANDEMICS

By Florence Débarre, Sebastian Bonhoeffer, Roland R. Regoes
Journal of the Royal Society – Interface
October 22, 2007

This article discusses a model to assess the impact of population structure and stochasticity on the development of vaccine-resistant strains of influenza caused by a vaccination campaign.

"The spread of H5N1 avian influenza and the recent high numbers of confirmed human cases have raised international concern about the possibility of a new pandemic. Therefore, antiviral drugs are now being stockpiled to be used as a first line of defence. The large-scale use of antivirals will however exert a strong selection pressure on the virus, and may lead to the emergence of drug-resistant strains. A few mathematical models have been developed to assess the emergence of drug resistance during influenza pandemics. These models, however, neglected the spatial structure of large populations and the stochasticity of epidemic and demographic processes. To assess the impact of population structure and stochasticity, we modify and extend a previous model of influenza epidemics into a metapopulation model which takes into account the division of large populations into smaller units, and develop deterministic and stochastic versions of the model. We find that the dynamics in a fragmented population is less explosive, and, as a result, prophylaxis will prevent more infections and lead to fewer resistant cases in both the deterministic and stochastic model. While in the deterministic model the final level of resistance during treatment is not affected by fragmentation, in the stochastic model it is. Our results enable us to qualitatively extrapolate the prediction of deterministic, homogeneous-mixing models to more realistic scenarios."

The full article can be found at: http://journals.royalsociety.org/content/9m10777mq4341gm5/?p=cb7a392733304b3dae3c02a9242d62bd&pi=11

Return to Top

DELSITE SUBMITS IND APPLICATION FOR GELVAC NASAL POWDER INFLUENZA VACCINE

Pharmaceutical Business Review
August 21, 2008

“DelSite has announced that DelSite Biotechnologies, its wholly-owned subsidiary, has filed an investigational new drug application with the FDA for its lead product candidate GelVac nasal powder H5N1 influenza vaccine.

The investigational new drug (IND) application is for a Phase I safety and immunogenicity study of this influenza vaccine in healthy volunteers. The filing initiates a 30-day review period by the FDA. The FDA may request additional information and clarification before the clinical study can begin.”

The full article can be found at: http://www.pharmaceutical-business-review.com/article_news.asp?guid=6D31E3E5-5C8B-415E-8B9E-7464D41D861D

Return to Top

INFLUENCE OF PRIOR INFLUENZA VACCINATION ON ANTIBODY AND B-CELL RESPONSES
By Sanae Sasaki, Xiao-Song He, Tyson H. Holmes, Cornelia L. Dekker, George W. Kemble, Ann. M. Arvin, Harry B. Greenberg
PLos One beta
August 22, 2008

“Currently two vaccines, trivalent inactivated influenza vaccine (TIV) and live attenuated influenza vaccine (LAIV), are licensed in the USA. Despite previous studies on immune responses induced by these two vaccines, a comparative study of the influence of prior influenza vaccination on serum antibody and B-cell responses to new LAIV or TIV vaccination has not been reported. During the 2005/6 influenza season, we quantified the serum antibody and B-cell responses to LAIV or TIV in adults with differing influenza vaccination histories in the prior year: LAIV, TIV, or neither. Blood samples were collected on days 0, 7–9 and 21–35 after immunization and used for serum HAI assay and B-cell assays. Total and influenza-specific circulating IgG and IgA antibody secreting cells (ASC) in PBMC were detected by direct ELISPOT assay. Memory B cells were also tested by ELISPOT after polyclonal stimulation of PBMC in vitro. Serum antibody, effector, and memory B-cell responses were greater in TIV recipients than LAIV recipients. Prior year TIV recipients had significantly higher baseline HAI titers, but lower HAI response after vaccination with either TIV or LAIV, and lower IgA ASC response after vaccination with TIV than prior year LAIV or no vaccination recipients. Lower levels of baseline HAI titer were associated with a greater fold-increase of HAI titer and ASC number after vaccination, which also differed by type of vaccine. Our findings suggest that the type of vaccine received in the prior year affects the serum antibody and the B-cell responses to subsequent vaccination. In particular, prior year TIV vaccination is associated with sustained higher HAI titer one year later but lower antibody response to new LAIV or TIV vaccination, and a lower effector B-cell response to new TIV but not LAIV vaccination.”

The full article can be found at: http://www.plosone.org/article/info%3Adoi%2F10.1371%

2Fjournal.pone.0002975

Return to Top

EVOLUTIONARY AND TRANSMISSION DYNAMICS OF REASSORTANT H5N1 INFLUENZA VIRUS IN INDONESIA
By Tommy Tsan-Yuk Lam, Chung-Chau Hon, Oliver G. Pybus, Sergei L. Kosakovsky Pond, Raymond Tze-Yeung Wong, Chi-Wai Yip, Fanya Zeng, Frederick Chi-Ching Leung
PLoS Pathogens
August 25, 2008

"In this study, we present phylogenetic evidences for the interlineage reassortment among H5N1 HPAI viruses isolated from humans, cats, and birds in Indonesia, and identify the potential genetic parents of the reassorted genome segments. Parsimony analyses of viral phylogeography suggest that the reassortant viruses may have originated from greater Jakarta and surroundings, and subsequently spread to other regions in the West Java province. In addition, Bayesian methods were used to elucidate the genetic diversity dynamics of the reassortant strain and one of its genetic parents, which revealed a more rapid initial growth of genetic diversity in the reassortant viruses relative to their genetic parent. These results demonstrate that interlineage exchange of genetic information may play a pivotal role in determining viral genetic diversity in a focal population. Moreover, our study also revealed significantly stronger diversifying selection on the M1 and PB2 genes in the lineages preceding and subsequent to the emergence of the reassortant viruses, respectively. We discuss how the corresponding mutations might drive the adaptation and onward transmission of the newly formed reassortant viruses."

The full article can be found at: http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1000130;jsessionid=D23002C6F4AEB1E58FB8AB5D74489EF1

Return to Top

H1N1 FLU VIRUSES GROWING MORE RESISTANT TO TAMIFLU
By Robert Roos
CIDRAP News (Center for Infectious Disease Research & Policy – University of Minnesota)
August 25, 2008

"With influenza season well under way in the southern hemisphere, one of the three kinds of seasonal influenza virus is becoming increasingly resistant to the antiviral drug oseltamivir (Tamiflu), the World Health Organization (WHO) reported last week.

Thirty-one percent (242 of 788) of influenza A/H1N1 isolates from 16 countries that were tested in recent months carried a mutation associated with oseltamivir resistance, the WHO said. In South Africa, all of the 107 isolates tested had this mutation, known as H274Y, the agency reported."

The full article can be found at: http://www.cidrap.umn.edu/cidrap/content/influenza/panflu/news/aug2508tamiflu.html

Return to Top

SUBSTRATE CLEAVAGE ANALYSIS OF FURIN AND RELATED PROPROTEIN CONVERTASES. A COMPARATIVE STUDY
Virus Weekly
August 26, 2008

'Substrate cleavage analysis of furin and related proprotein convertases. A comparative study,' is now available. "We present the data and the technology, a combination of which allows us to determine the identity of proprotein convertases (PCs) related to the processing of specific protein targets including viral and bacterial pathogens. Our results, which support and extend the data of other laboratories, are required for the design of effective inhibitors of PCs because, in general, an inhibitor design starts with a specific substrate."

"Seven proteinases of the human PC family cleave the multibasic motifs R-X-(R/K/X)-R downward arrow and, as a result, transform proproteins, including those from pathogens, into biologically active proteins and peptides. The precise cleavage preferences of PCs have not been known in sufficient detail; hence we were unable to determine the relative importance of the individual PCs in infectious diseases, thus making the design of specific inhibitors exceedingly difficult. To determine the cleavage preferences of PCs in more detail, we evaluated the relative efficiency of furin, PC2, PC4, PC5/6, PC7, and PACE4 in cleaving over 100 decapeptide sequences representing the R-X-(R/K/X)-R downward arrow motifs of human, bacterial, and viral proteins. Our computer analysis of the data and the follow-on cleavage analysis of the selected full-length proteins corroborated our initial results thus allowing us to determine the cleavage preferences of the PCs and to suggest which PCs are promising drug targets in infectious diseases."

"Our results also suggest that pathogens, including anthrax PA83 and the avian influenza A H5N1 (bird flu) hemagglutinin precursor, evolved to be as sensitive to PC proteolysis as the most sensitive normal human proteins."

The full article can be found at: (A.G. Remacle, et. al., “Substrate cleavage analysis of furin and related proprotein convertases. A comparative study”. Journal of Biological Chemistry, 2008;283(30):20897-906). Link not available.

Return to Top

INFLUENZA IMMUNIZATION AND SUBSEQUENT DIAGNOSES OF GROUP A STREPTOCOCCUS-ILLNESSES AMONG U.S. ARMY TRAINEES, 2002-2006
Drug Week
August 29, 2008

United States Army Center for Health Promotion and Preventive Medicine [CHPPM] reports the results of a study examining “the association between influenza immunization and subsequent diagnosis of group A streptococcus (GAS)-illness in Army recruits during influenza seasons 2002-2006. A case-control study was employed with cases as trainees with outpatient GAS diagnosis (ICD-9-CM codes: 034.0, 035, 038.0, 041.01, 320.2, 390-392, 482.31) during the influenza season, and controls as trainees with no outpatient GAS diagnosis during the influenza season."

"Primary exposure was influenza immunization during 1st September to 30th April of each season. Estimated protective effects of influenza immunization against GAS-illness ranged from 50% to 77%."

"A strong protective effect was suggested for Army trainee influenza immunization on the diagnosis of GAS-illness."

The full article can be found at: (S.E. Lee, et. al., “Influenza immunization and subsequent diagnoses of group A streptococcus-illnesses among U.S. Army trainees”, 2002-2006. Vaccine, 2008;26(27-28):3383-6). Link not available.

Return to Top

END of CB Daily Report.

Send subscription requests, unsubscribing requests, questions and comments to**:**

Sandy Banks: Sandra.Banks@anser.org

Steve Tesko: Steve.Tesko@anser.org

Heather Williams: Heather.Williams@anser.org

Suzanne Martinez: Suzanne.Martinez@anser.org